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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/823,263	LATTA, PAUL P.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-14 are pending.

2. Applicant's election without traverses of human as spices of mammal , intraportal as species of implanting step in the reply filed on 10/12/04 is acknowledged.

Claims 1-14 read on a method of treating diabetes in mammal, wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells, wherein administering is intaportal under consideration in the instant application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

4. Applicant notes that an IDS was submitted with the prior application 10/660,924. However these citations have been crossed out as said references cited in said parent application cannot be found. Applicant is invited to resubmit such references to complete the instant file. The examiner apologizes for any inconvenience to applicant for having to resubmit such documents.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 6 and 11 recites the limitation "administering a curative dose" There is insufficient antecedent basis for this limitation in the claim. The preamble of the base claim 1 recites " a method of treating diabetes", not a method of curing diabetes.

B. Claim 6 is indefinite and ambiguous in the recitation of "..wherein said tolerizing and curative doses are porcine". It is unclear what Applicant means by this phrase, since " doses" can not be porcine.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses the effects of the implanting of insulin-producing cells on the level of blood glucose using streptozotocin-induced diabeties in murine experimental model. (See Examples 1-2 in particular). Examples 3-7 in the instant Specification are prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed. The specification does not adequately teach how to effectively treat diabetes in mammal , wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells wherein administrating step is intaportal . Moreover, the specification does not teach whether administering of second i.e. curative dose that is one or two orders of magnitude more than tolerizing dose will be tolerated (i.e. not rejected) in human. Roep et al (Nature Reviews, 2004, v.4, pages 989-997) teaches that despite more than two decades of productive research, we are still yet to define an initiating autoantigen for human disease, to determinethe precise mechanism of β-cell destruction in human and to design invention thatprevent or cure type I diabetes. Studying the pathogenesis of diabetes in human is difficult. No animal model had

been developed that shows a reproducibly high incidence of disease in a timely experimental manner. Many of the preventive therapies that seems to be promising in mouse models did not show similar efficacy in human patient. We believed that it is necessary to re-evaluate and consider at a higher level the apparent difference in the immunology and biology of diabetes between mice and men. (see entire documewnt, Abstract, pages 989, 990 and Table 1 in particular). Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Teuveson et al., (Immun. Review 1993, N136, pages 101-107) teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in human (see page 100 in particular). Teuveson et al., further teach that " however today's small animal models seem to be insufficient to produce data for clinical decision-making" and further raises doubt as to whether large animal models can be applied to clinical situations, due to species-specific reactions to treatment (see page 101 in particular). Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Moreover, since the a method of treating diabetes in mammal, wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells can be species- and model-dependent (see Van Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vivo* murine data accurately reflects the relative any mammal and human efficacy of the claimed therapeutic strategy. Van Noort et al., further indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

Thus, as has been discussed supra, the state of the art is that it is unpredictable form the *in vivo* murine data disclosed in the specification as whether the instant invention can be used for the *in vivo* treatment of diabetes in any mammals including human. Therefore, it is not clear that the skilled artisan could predict the efficacy a method of treating diabetes in mammal, wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of the claimed method of treating diabetes in mammal, wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells are fraught with uncertainties.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a method of treating diabetes in mammal, wherein mammal is human, comprising implanting a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-4 and 6 -14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425764 or US Patent 5,629,194 each in view Posselt et al (Diabetes, 1992, v.41, pages 771-775) as is evidenced by the disclosure of Specification on overlapping pages 12-13.

US Patent '017 teaches a method of treating diabetes in a mammal comprising implanting insulin-producing cells encapsulated in a biologically compatible membrane (see entire document, Abstract and columns 6, 8, 9 –14 and Example 12 in particular) . US Patent '017 teaches that insulin producing cells are pancreatic islet cells from primary cell source (see columns 8 and 11 in particular). US Patent '017 teaches that pancreatic islet cells are from the

same species as the mammal and are implanted interperitoneally into the tissue of a mammal beneath the kidney capsule (see overlapping columns 13-14 and Example 2 in particular). US Patent '017 teaches that encapsulation of said insulin-producing cells in biologically compatible membrane for success of implantation is well known in the art (see column 12 and Example 12 in particular).

US Patent '764 teaches a method of treating diabetes in a mammal comprising implanting insulin-producing cells encapsulated in a biologically compatible membrane (see entire document, Abstract and overlapping columns 5-6 in particular). US Patent '764 teaches that insulin producing cells are pancreatic islet cells (see column 1 and 4 in particular). US Patent '764 teaches that cells are implanted interperitoneally (see column 5 in particular).

US Patent '194 teaches a method of treating diabetes in mammal comprising implanting insulin-producing cells encapsulated in a biologically compatible membrane (see entire document, Abstract overlapping columns 7-8 , 12 and Example II in particular). US Patent '764 teaches that insulin producing cells are pancreatic islet cells (see column 8 in particular). US Patent '764 teaches that cells are implanted intaportal (see column 7 in particular). US Patent '194 teaches administration of one or more anti-inflammatory agent at the dosage sufficient to achieve the desired therapeutic effect. US Patent '194 teaches that said agent can be administered prior to at the same time or subsequent to administration of insulin-producing cells (see overlapping columns 14-15 in particular).

US Patent '017 or US Patent ' 764 or US Patent '194 does not explicitly teaches a method of treating diabetes in a mammal comprising administration two doses of insulin-secreting cells one tolerizing and one curative wherein tolerizing doze is one order less than curative.

Posselet et al., teach that the important goal in the treatment of insulin-dependent diabetes by pancreatic islet transplantation is the development of strategies that allow permanent survival of pancreatic islet without continuous host immunosuppression. Posselet et al., further teach a strategy comprising two step process : first administering a small dose of cells that induces an unresponsive state, i.e. tolerizing dose and then administering fully therapeutic dose, at another site (see entire document, Abstract in particular). Posselet et al., teach that said strategy permits the survival of pancreatic islet transplant.

The Specification on overlapping pages 12-13 disclosed that curative dose is fully therapeutic dose.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Posselt at al. to those of US Patent '017 or US Patent ' 764 or US Patent '194 to obtain a claimed method of treating diabetes in a mammal comprising

administration two doses of insulin-secreting cells one tolerizing and one curative wherein tolerizing doze is one order less than curative

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because a strategy comprising two step process : first administering a small dose of cells that induces an unresponsive state, i.e. tolerizing dose and then administering fully therapeutic dose, at another site permits the survival of pancreatic islet transplant as taught by Posselet et al. Said strategy can used in the method of treating diabetes in a mammal, comprising implanting pancreatic islet, taught by US Patent '017 or US Patent ' 764 or US Patent '194. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 8-14 are included because it would be conventional and within the skill of the art to : (i) determine the proper pore size for the permselective membrane or (ii) to determine the optimum dosage and means of administration of insulin-secreting cells in an absent of a showing of unobvious property. Moreover, Applicant acknowledge that one of ordinary skill in the art can readily determine the proper pore size for the permselective membrane (see page 8, line 13-20 of the instant Specification in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or means of administration involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

11. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425764 or US Patent 5,629,194 each in view Posselt et al (Diabetes, 1992, v.41, pages 771-775) as applied to claims 1-4 and 6-14 above, and further in view of US Patent 5,529,914.

The teaching of US Patent " 017, US Patent ' 764 , US Patent' 194 and Posselt et al., have been discussed, supra.

The combined references do not explicitly teachers a method of treating diabetes in a mammal comprising implanting insulin-secreting cells, wherein insulin-secreting cells are encapsulated in a biologically compatible membrane wherein said membrane comprises polyethylene glycol (PEG).

US Patent '914 teaches a new type of biocompatible membrane as a covering to encapsulate biological materials, comprising PEG that is acceptable for implants in mammalian. (see entire document, Abstract in particular). US Patent '914 teaches that various types of cells can be encapsulated in said biocompatible membrane and that said encapsulation will prevent rejection of encapsulated cells during transplantation (see column 10 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '914 to those of US Patent " 017, US Patent ' 764 , US Patent' 194 and Posselt et al., to obtain a claimed method of treating diabetes in a mammal comprising implanting insulin-secreting cells, wherein insulin-secreting cells are encapsulated in a biologically compatible membrane wherein said membrane comprises polyethylene glycol (PEG).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because encapsulation of cells in biologically compatible membrane comprising PEG will prevent rejection of encapsulated cells during transplantation as taught by US Patent '914. Said type of biocompatible membrane can be used to substitute the different type of biocompatible membrane for successful implantation of insulin-producing cells in the method of treating diabetes taught by combined references of US Patent " 017, US Patent ' 764 , US Patent' 194 and Posselt et al. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 24, 2005

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